

Cerebral Perfusion in AD and Subcortical Ischemic Vascular Dementia using Arterial Spin Labeled MRI

N. Schuff^{1,2}, S. Matsumoto³, J. Kmiecik², C. Studholme^{1,2},
A.T. Du¹, B.L. Miller⁴, J.H. Kramer⁵, W.J. Jagust⁶, H.C. Chui⁷,
F. Ezekiel^{1,2} and M.W. Weiner^{1,2,8}

¹Magnetic Resonance Unit, Department of Veterans Affairs Medical Center, San Francisco; Departments of ²Radiology, ⁴Neurology, ⁵Psychiatry, and ⁸Medicine, University of California at San Francisco, U.S.A.; ³Federal Patent Office of Japan, Tokyo, Japan; ⁶Department of Neurology, University of California at Davis, U.S.A.; ⁷Department of Neurology, University of Southern California, Los Angeles, U.S.A.

Summary

The goals of this study were: 1) To compare the effects of Alzheimer's disease (AD) and subcortical ischemic vascular dementia (SIVD) on brain perfusion and 2) to determine the relationship between cortical hypoperfusion and subcortical vascular disease, measured as white matter lesions (WML). Eight mildly demented patients with SIVD (77 ± 8 years, 26 ± 3 MMSE) and 14 patients with AD of comparable age and dementia severity were compared to 18 cognitively normal elderly. All subjects had perfusion measured using multiplanar arterial spin labeled MRI, which does not require injection of a contrast agent. Both, AD and SIVD showed marked hypoperfusion primarily in frontal ($p < 0.001$) and parietal ($p < 0.001$) lobe gray matter, independent of atrophy. Further, WML were associated with hypoperfusion in frontal ($p < 0.02$) and parietal ($p < 0.002$) lobe gray matter, independent of diagnosis. In conclusion, hypoperfusion implies that function of remaining brain tissue is reduced in SIVD and AD and subcortical vascular disease can contribute either primary or secondary to cortical dysfunction.

Introduction

Subcortical ischemic vascular dementia (SIVD) and Alzheimer's disease

(AD) cause neurodegeneration in different regions of the brain. The reduced neuronal activity associated with these conditions is associated with reduced cerebral blood flow and brain tissue perfusion. SPECT and PET brain imaging studies of perfusion reported patchy patterns of regional hypoperfusion in SIVD⁽¹⁾, while a more characteristic pattern of regional hypoperfusion, involving primarily the posterior cingulate and the lateral temporoparietal cortex was found in AD.⁽²⁾ However, hypoperfused regions in SIVD and AD can coincide with regions of brain atrophy, especially in advanced stages of diseases. Therefore, perfusion studies should be corrected for underlying structural variations. Recently, we⁽³⁾ and other researchers⁽⁴⁾ applied pulsed arterial spin labeling (PASL) MRI⁽⁵⁾, which uses magnetically labeled blood water as endogenous tracer, to study brain perfusion in AD. Since PASL MRI and structural MRI can easily be obtained in rapid succession within one scan session, corrections of perfusion for underlying structural variations should be easier to accomplish than with SPECT and PET studies, which are obtained separately from MRI. The main goal of this study was to measure the effects of SIVD and AD on brain perfusion, including careful corrections for structural variations based on tissue segmented MRI data. Based on previous reports from SPECT and PET studies of perfusion, we predicted that SIVD would be associated with marked hypoperfusion in the frontal cortex, while AD would exhibit hypoperfusion predominantly in the posterior cortex. In addition, we sought to determine the relationship between cortical hypoperfusion and subcortical vascular disease, measured by white matter lesions (WML) on MRI.

Material and Methods

Demographics: This study included 8 patients with SIVD (mean age 77 ± 8 years, 2 women and 6 men), 14 patients with AD (mean age 74 ± 5 years, 6 women and 8 men), and 18 cognitive normal (CN) subjects (mean age 73 ± 8 years, 8 women and 10 men). AD was diagnosed according to NINCDS/ADRDA criteria and SIVD was diagnosed according to the criteria of the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC). Both SIVD and AD patients were mildly demented based on Mini-Mental State Examination (MMSE) scores of 26.4 ± 2.8 for SIVD and 22.9 ± 4.7 for AD, compared to 29.5 ± 0.5 for CN subjects. Furthermore, the amount of WML as percent of intracranial volume was on average $1.9 \pm 1.1\%$ in patients with SIVD and $0.4 \pm 0.2\%$ in patients with AD, compared to $0.5 \pm 0.5\%$ in CN subjects. All subjects gave written informed consent before participating in the study, which was approved by the Committees of Human Research at the University of California, San Francisco and Davis. *MRI:* Subjects had perfusion and structural MRI scans less than 30 minutes

apart on a 1.5 Tesla MR scanner. Perfusion was measured using a multislice QUIPSSII⁽⁵⁾-modified EPSTAR⁽⁶⁾ sequence with 6 contiguous and 9mm thick slices and 2.0mm² inplane resolution. Other parameters of the perfusion sequence were: 1700 ms repetition time, 15 ms echo time, and 1500ms transit time for labeled water to flow into the image plans; 50 interleaved tag + control averages; 90mm tagging slab, positioned 65mm inferior to the center of the lowest image plane. In addition to perfusion, structural MRI data were obtained using MPRAGE (TR/TE/TI=10/4/300ms, 1.5mm³ resolution) and double-spin echo sequences (TR/TE1/TE2 = 5000/20/80ms, 3.0mm³ resolution). Tissue segmentation of gray matter, white matter, and CSF was based on simultaneous evaluation of the T1-, T2-, and density-weighted image contrasts. Furthermore, WML volumes were determined to establish subcortical vascular disease. The main brain lobes on each subject's MRI data were identified using high dimensional brain warping of an atlas brain to the individual brains. Finally, perfusion and structural MR images were registered and the tissue-segmented images were blurred to the resolution of perfusion MRI to estimate the tissue composition in each MRI perfusion voxel. *Statistics:* In order to obtain perfusion separately of gray matter and white matter in the main brain lobes, variation of perfusion intensity was regressed against tissue composition for all voxel within a lobe region. Perfusion of "pure" gray matter and white matter was then estimated by extrapolating the regressions to 100% gray matter or white matter voxels, respectively, as previously described by the authors for MR spectroscopic imaging data⁽⁷⁾. MANOVA was used to determine overall the effects of group, WML, and regions on perfusion, followed by Scheffe post-hoc tests to account for multiple comparisons. Age and MMSE were used as covariates when appropriate.

Results

The Table lists the main results of gray matter perfusion (in ml/100mg tissue/min) and volumes (in % intracranial volume) of the main lobes, separately for each group. There was an overall effect of diagnosis on perfusion in frontal lobe gray matter ($F_{3,36}=11.5$; $p < 0.002$) and parietal lobe gray matter ($F_{3,36}=15.6$; $p < 0.001$) with a trend ($p = 0.08$) in temporal and occipital lobe gray matter. Effects of diagnosis on perfusion remained significant after accounting for variations of WML among groups. Post-hoc tests revealed that perfusion was significantly reduced in frontal and parietal lobe gray matter in both SIVD and AD patients when compared to CN subjects. However, differences of perfusion between SIVD and AD were not significant. In addition to diagnosis, WML was significantly associated with variations of perfusion across all groups. WML accounted for about 11% ($F_{4,35}=6.6$; $p < 0.02$) variation

Table. Perfusion and volume of gray matter tissue in the major brain lobes and differences between demented patients and normal elderly subjects.

	SIVD	AD	Normal	SIVD vs. Normal	AD vs. Normal	SIVD vs. AD
Perfusion¹						
Frontal	30.1 ± 11.1 [‡]	31.9 ± 8.4 [‡]	43.7 ± 6.1	-31%	-27%	-6%
Parietal	27.6 ± 9.1 [‡]	33.8 ± 9.0 [‡]	45.5 ± 7.6	-39%	-26%	-18%
Temporal	29.2 ± 9.7	35.3 ± 11.7	40.8 ± 14.8	-28%	-13%	-17%
Volumes²						
Frontal	14.0 ± 1.3 [‡]	14.1 ± 1.2 [‡]	15.1 ± 0.9	-7%	-7%	-1%
Parietal	6.2 ± 0.5 [‡]	6.3 ± 0.5 [‡]	7.1 ± 0.5	-13%	-11%	-2%
Temporal	8.4 ± 0.9 [‡]	8.7 ± 0.7 [‡]	9.8 ± 0.7	-14%	-11%	-3%

¹ Gray matter perfusion in units of ml/100mg tissue/min;

² Gray matter volume in percent of intracranial volume;

[‡] p < 0.05 compared to cognitive normal (CN) controls;

of perfusion in the frontal lobe gray matter, compared to 32% variation explained by diagnosis. Similarly, WML accounted for about 18% ($F_{4,35}=12.5$; $p < 0.002$) variation of perfusion in parietal lobe gray matter, compared to 30% variation explained by diagnosis. Similar to perfusion, there was an overall effect of diagnosis on volumes of frontal ($F_{3,36}=7.1$; $p < 0.003$) and parietal gray matter ($F_{3,36}=15.5$; $p < 0.001$). There was further a significant effect of diagnosis on temporal lobe gray matter volume ($F_{3,36}=14.4$; $p < 0.001$), but not on occipital lobe gray matter volume ($F_{3,36}=3.1$; $p = 0.06$). WML and gray matter volume were associated ($F_{4,35}=5.9$; $p = 0.02$) only in the parietal lobe, with WML accounting for about 8% variation of volume compared to 44% variation due to diagnosis. This contrasted results from perfusion, which indicated that WML had an effect on perfusion also in the frontal lobe.

Conclusions

The main finding of this study was substantial hypoperfusion in both frontal and parietal cortex in SIVD and AD, despite relatively mild stages of dementia. Furthermore, as perfusion values were derived from estimates of 100% gray matter and white matter tissue, differences of brain atrophy between patients and normal subjects no longer explain hypoperfusion in these patients. Therefore, these tissue corrected perfusion measurements imply that the function of remaining brain tissue in SIVD and AD is reduced. However, hypoperfusion in the frontal cortex in AD was an unexpected finding, conflicting with our initial hypothesis and with other perfusion studies, reporting involvement of predominantly posterior brain regions in AD. There are several explanations for this

finding. First, the mildly demented AD patients in this study were a clinically heterogeneous group, including patients with dysexecutive symptoms. Clinical heterogeneity has been correlated with heterogeneity in the regional distribution of AD pathology, which can involve frontal lobe pathology.⁽⁸⁾ The finding of frontal lobe atrophy in these patients further supports the notion of a heterogeneous AD patient group. Second, it is possible that the AD patients presented mixed etiologies, including cortical micro-infarctions and amyloid angiopathy. Mixed etiologies are common in older AD patients⁽⁹⁾. Eventually, it will be necessary to obtain autopsy information to exclude micro-infarctions, cerebral amyloid angiopathy, and concurrent SIVD as potential cause of frontal lobe hypoperfusion in AD.

Another important finding was the association between subcortical WML and cortical perfusion. This observation may also explain the unexpected finding of hypoperfusion in the frontal cortex in AD, since many AD patients presented some WML. There are several possible interpretations to this finding. First, subcortical infarctions may be responsible – at least in part – for cortical neurodegeneration and secondary hypoperfusion. A second possibility is that WML represent generalized cerebrovascular disease, possibly causing hypoperfusion, which then leads secondarily to cortical atrophy. Additional studies will be necessary to further elucidate the mechanisms that cause WML related cortical hypoperfusion.

In conclusion, hypoperfusion implies that function of brain tissue initially spared from atrophy is reduced in SIVD and AD and subcortical vascular disease can induce either primary or secondary cortical dysfunction.

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